UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/823,784	04/14/2004	Karen Uhlmann	3035-101	4952

46002 7590 02/28/2008

JOYCE VON NATZMER
PEQUIGNOT + MYERS LLC
200 Madison Avenue
Suite 1901
New York, NY 10016

EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
02/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/823,784	UHLMANN ET AL.	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-20 and 22-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-20 and 22-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed January 17, 2008. This action is made FINAL.

Claims 1-5, 7-20, and 22-39 are currently pending. Claims 1, 8, 9, 12, 18, 22-24, and 38 have been amended. Claim 39 is newly presented.

Withdrawn Objections

2. The objection made to the abstract in section 4 of the Office Action of July 17, 2007 is withdrawn in view of the amendments made to the abstract.

The objection made to the specification in section 4 of the Office Action of July 17, 2007 is withdrawn in view of the amendments made to the specification.

The objection made to the claim 22 in section 5 of the Office Action of July 17, 2007 is withdrawn in view of the amendments made to the claims.

Withdrawn Rejections

3. Several of the rejections made under 35 USC 112 2nd paragraph in section 6 of the Office Action of July 17, 2007 are withdrawn in view of amendments made to the claims and/or Applicants arguments presented on pages 16-19 of the response filed January 17, 2008. All rejections not reiterated herein are considered withdrawn.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 37 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 recites the limitation "said methylated nucleotide". There is insufficient antecedent basis for this limitation in the claims because although previous claims refer to detecting whether said nucleotide is methylated or not methylated, the previous claims do not refer to a "methylated nucleotide". It is suggested the claims be amended to overcome this rejection by e.g., replacing "said" with "a".

Response To Arguments

In the response filed January 17, 2008, the Applicants stated (page 17) that they have amended claim 37 to overcome the rejection. However it is noted that no amendments have been made to claim 37. Therefore the rejection is maintained.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-5, 7-9, 11-12, 19-20, 22-24, 26-33, and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al (Electrophoresis 1999) in view of Nyren et al (U.S. Patent 6258568 Issued 2001).

Regarding Claims 1-5, 7-9, 11, 22, 27, 30-31, 33, and 36-37 Uhlmann et al teach a method for identifying methylated cytosines comprising treating a sample containing genomic DNA derived from blood and tumor tissue with sodium bisulfite and amplifying the sample by PCR. Uhlmann et al further teach that the amplified nucleic acids were sequenced by the dideoxynucleotide chain termination method determine the methylation state of the amplified product (Page 1750-1751).

Uhlmann et al do not teach a method wherein the amplification primer has a label that forms an anchor for removal of single stranded amplified nucleic acid molecules.

Further Uhlmann does not teach that the amplified nucleic acids were sequenced using a real-time sequencing method.

However, Nyren et al teach a real time sequencing method called pyrosequencing that can be used to identify a base at a predetermined position in a DNA sample using an extension primer, which hybridizes immediately adjacent to the target position. The DNA sample and extension primer are subjected to a polymerase reaction in the presence of each dNTP. The dNTPs are successively added to the same sample primer mixture and the dNTPs will only become incorporated and release pyrophosphate (PPi) if it is complementary to the base in the target position. When the PPi is released a certain amount of light gets released that is equivalent to the amount of incorporated nucleotides. The unincorporated dNTPs get degraded (Column 2, lines 25-42). Nyren further teach to aid in the separation of a single stranded sample DNA from its complementary strand the sample DNA may be provided with means for attachment to a solid support. Nyren teaches that one or more of the PCR primers may carry a functional group such as a biotin which permits subsequent immobilization (Column 8, lines 22-31). Thus Nyren teaches a step of converting an amplification product into single stranded amplification nucleic acid molecules.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Uhlmann et al by using pyrosequencing to determine the sequence of the amplified DNA fragment as suggested by Nyren. Specifically Nyren et al teaches that the benefit of performing pyrosequencing over other sequencing methods such as the enzymatic chain

termination method of Sanger is that pyrosequencing enables a base to be identified in a target position and DNA to be sequenced simply and rapidly while avoiding the need for electrophoresis and use of harmful radiolabels (Column 1, lines 60-64). Nyren further teach that other sequencing methods which rely on electrophoresis are not well suited for large-scale genome projects or clinical sequencing where high throughput is needed (Column 1, lines 15-30). However the pyrosequencing method of Nyren opens up the possibility for an automated approach for large scale, non-electrophoretic sequencing procedures which allow for continuous measurement of the progress of the polymerization reaction with time. The method of Nyren also has the advantage that multiple samples may be handled in parallel (Column 9, lines 4-6).

Regarding Claim 12 as noted in the MPEP 211.02, "a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, the steps present in the method are able to stand-alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language

of "a method for the diagnosis of a pathological condition or the predisposition for a pathological condition" merely sets forth the intended use or purpose of the claimed method, but does not limit the scope of the claims.

Regarding Claims 12, 19-20, 23-24, 26, 28-29, Uhlmann et al teach a method comprising treating a sample containing genomic DNA derived from blood and tumor tissue with sodium bisulfite and amplifying the sample by PCR. Uhlmann et al further teach that the amplified nucleic acids were sequenced by the dideoxynucleotide chain termination method determine the methylation state of the amplified product (Page 1750-1751).

Uhlmann et al do not teach a method wherein the amplification primer has a label that forms an anchor for removal of single stranded amplified nucleic acid molecules. Further Uhlmann does not teach that the amplified nucleic acids were sequences using a real-time sequencing method.

However, Nyren et al teach a real time sequencing method called pyrosequencing that can be used to identify a base at a predetermined position in a DNA sample using an extension primer, which hybridizes immediately adjacent to the target position. The DNA sample and extension primer are subjected to a polymerase reaction in the presence of each dNTP separately and the dNTPs will only become incorporated and release pyrophosphate (PPi) if it is complementary to the base in the target position. When the PPi is released a certain amount of light gets released that is equivalent to the amount of incorporated nucleotides. The unincorporated dNTPs get degraded (Column 2, lines 25-42). Nyren further teach to aid in the separation of a

single stranded sample DNA from its complementary strand the sample DNA may be provided with means for attachment to a solid support. Nyren teaches that one or more of the PCR primers may carry a functional group such as a biotin which permits subsequent immobilization (Column 8, lines 1-31). Thus Nyren teaches a step of converting an amplification product into single stranded amplification nucleic acid molecules.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Uhlmann et al by using pyrosequencing to determine the sequence of the amplified DNA fragment as suggested by Nyren. Specifically Nyren et al teaches that the benefit of performing pyrosequencing over other sequencing methods such as the enzymatic chain termination method of Sanger is that pyrosequencing enables a base to be identified in a target position and DNA to be sequenced simply and rapidly while avoiding the need for electrophoresis and use of harmful radiolabels (Column 1, lines 60-64). Nyren further teach that other sequencing methods which rely on electrophoresis are not well suited for large-scale genome projects or clinical sequencing where high throughput is needed (Column 1 lines 15-36). However the pyrosequencing method of Nyren opens up the possibility for an automated approach for large scale, non-electrophoretic sequencing procedures which allow for continuous measurement of the progress of the polymerization reaction with time. The method of Nyren also has the advantage that multiple samples may be handled in parallel (Column 9, lines 4-6).

Regarding Claim 32 as noted in the MPEP 211.02, the courts have stated that "a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." In the present situation, the steps present in the method are able to stand-alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of "a method for generating new nucleotide pairing partners upon amplification of at least one nucleic acid molecule for the detection of the methylation status of nucleotides of said nucleic acid molecule" merely sets forth the intended use or purpose of the claimed method, but does not limit the scope of the claims.

Regarding Claim 32, Uhlmann et al teach a method comprising treating a sample containing genomic DNA derived from blood and tumor tissue with sodium bisulfite and amplifying the sample by PCR. Uhlmann et al further teach that the amplified nucleic acids were sequenced by the dideoxynucleotide chain termination method determine the methylation state of the amplified product (Page 1750-1751).

Uhlmann et al do not teach a method wherein the amplification primer has a label that forms an anchor for removal of single stranded amplified nucleic acid molecules. Further Uhlmann does not teach that the amplified nucleic acids were sequences using a real-time sequencing method.

However, Nyren et al teach a real time sequencing method called pyrosequencing that can be used to identify a base at a predetermined position in a

DNA sample using an extension primer, which hybridizes immediately adjacent to the target position. The DNA sample and extension primer are subjected to a polymerase reaction in the presence of each dNTP separately and the dNTPs will only become incorporated and release pyrophosphate (PPi) if it is complementary to the base in the target position. When the PPi is released a certain amount of light gets released that is equivalent to the amount of incorporated nucleotides. The unincorporated dNTPs get degraded (Column 2, lines 25-42). Nyren further teach to aid in the separation of a single stranded sample DNA from its complementary strand the sample DNA may be provided with means for attachment to a solid support. Nyren teaches that one or more of the PCR primers may carry a functional group such as a biotin which permits subsequent immobilization (Column 8, lines 1-31). Thus Nyren teaches a step of converting an amplification product into single stranded amplification nucleic acid molecules.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Uhlmann et al by using pyrosequencing to determine the sequence of the amplified DNA fragment as suggested by Nyren. Specifically Nyren et al teaches that the benefit of performing pyrosequencing over other sequencing methods such as the enzymatic chain termination method of Sanger is that pyrosequencing enables a base to be identified in a target position and DNA to be sequenced simply and rapidly while avoiding the need for electrophoresis and use of harmful radiolabels (Column 1 lines 60-64). Nyren further teach that electrophoresis is not well suited for large-scale genome projects or clinical

sequencing where high throughput is needed (Column 1, lines 15-36). However the pyrosequencing method of Nyren opens up the possibility for an automated approach for large scale, non-electrophoretic sequencing procedures which allow for continuous measurement of the progress of the polymerization reaction with time. The method of Nyren also has the advantage that multiple samples may be handled in parallel (Column 9, lines 4-6).

7. Claims 13-16, 18 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al (Electrophoresis 1999) in view of Nyren et al (U.S. Patent 6258568 Issued 2001) as applied to claim 12 above, and in further view of Herman (U.S. Patent 5786146 Issued 1998).

The teachings of Uhlmann et al and Nyren et al are presented above.

The combined references do not teach that the methylation status is used to diagnose a pathological condition such as cancer, a neurodegenerative disease or another neurological disorder. The combined references also do not teach that the methylation status is used diagnose cancer that is a primary tumor, a metastasis or a residual tumor. The combined references do not teach that the primary tumor is a glioma selected from the group comprising: astrocytoma, oligodendroglioma, an oligoastrocytoma, a glioblastoma, and a pilocytic astrocytoma. The combined references also do not teach that the neurological disorder is selected from the group

comprising: Prader-Willi-Syndrome, Angelman-Syndrome, Fragile-X-Syndrome, or ATR-X-Syndrome.

However, Herman et al teaches that the detection of methylated CpG containing nucleic acid is indicative of several disorders. Such disorders include but are not limited to low grade astrocytoma, anaplastic astrocytoma, glioblastoma, medulloblastoma, colon cancer, lung cancer, renal cancer, leukemia, breast cancer, prostate cancer, endometrial cancer and neuroblastoma. Identification of methylated CpG status is also useful for detection and diagnosis of genomic imprinting, fragile X syndrome and X-chromosome inactivation (Column 10, lines 49-58).

Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Uhlmann and Nyren to diagnose pathological disorders. It was well known in the art at the time the invention was made that the detection of methylated sequences is indicative of several pathological disorders. Accordingly, one of ordinary skill in the art would have been motivated to use the method of Uhlmann and Nyren in order to have achieved the advantage of being able to diagnose these diseases.

8. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al ((Electrophoresis 1999) in view of Nyren et al (U.S. Patent 6258568) and Herman (U.S. Patent 5786146 Issued 1998) as applied to claims 12 and 38 above, and in further view of Feinberg (Pub No. US 2003/0232351).

The teachings of Uhlmann, Nyren, and Herman are presented above.

The combined references do not teach a method used to diagnose neurodegenerative diseases such as Alzheimer's disease, Parkinson disease, Huntington disease, or Rett-Syndrome.

However, Feinberg teaches a method of determining a disease state in a subject by determining DNA methylation status. Although the disease state is often cancer, the methods taught by Feinberg also include Alzheimer's disease and Parkinson's disease (Paragraph 0029).

Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the method that Uhlmann, Nyren and Herman used to diagnose primary tumors, to also diagnose neurodegenerative diseases. It was well known in the art at the time the invention was made that the detection of methylated sequences is indicative of certain neurodegenerative diseases. Accordingly, one of ordinary skill in the art would have been motivated to use the method of Uhlmann, Nyren and Herman in order to have achieved the advantage of being able to diagnose these diseases.

9. Claims 10, 25, 34, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al ((Electrophoresis 1999) in view of Nyren et al (U.S. Patent 6258568) as applied to claims 1 and 12 above, and in further view of Sylvan (US Patent 7078168 Filed 2/2002).

The teachings of Uhlmann and Nyren are presented above.

The combined references do not teach a method further comprising calculating a frequency of methylated nucleotides from the results of said real time sequencing. Further the combined references do not teach a method wherein an allele frequency of 5% can be detected.

However, Sylvan teaches a method of determining the frequency of an allele in a population of nucleic acid molecules. The method comprises performing primer extension reactions using a primer which binds at a predetermined site located in nucleic acid molecules and obtaining a pattern of nucleotide incorporation (Abstract). Specifically Fig 4a depicts graphically relative peak heights from a pyrosequencing reaction plotted against allele frequency. After the pyrosequencing was performed, the resulting peak heights were plotted versus expected allele frequency and a linear relationship between the 2 was demonstrated (Column 5, lines 7-16). As you can see an allele frequency were detected. Regarding newly presented claim 39, Sylvan does not exemplify a method wherein an allele frequency of 5% is detected with a standard deviation of not more than 1%, however claim 39 limits claim 34 which does not actually require detecting an allele frequency of 5%. The wherein clause in claim 34 is conditional in view of the "can be" language. Therefore the claims actually only require detecting an allele frequency.

Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method that Uhlmann and Nyren by further calculating the frequency of methylated nucleotides from the results of the pyrosequencing as suggested by Sylvan. The method of Sylvan is advantageous in

that it determines the exact sequence of a nucleic acid fragment while directly measuring the amount of nucleotide incorporated. Using this method is it possible to obtain accurate, cost effective, and rapid information on allele frequencies (Column 22, lines 39-67 and Column 23, lines 1-4).

10. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al ((Electrophoresis 1999) in view of Nyren et al (U.S. Patent 6258568) as applied to claim 1 above, and in further view of Laird (US 2002/0086324 Filed 10/2001).

The teachings of Uhlmann and Nyren are presented above.

The combined references do not teach a method wherein the amplification primer does not comprise CpG.

However, Laird teaches a method wherein a genomic DNA is provided that has mixed methylation status. The sample is converted in a standard sodium bisulfite reaction and the mixed products are amplified by a PCR reaction using primers that do not overlap any CpG dinucleotides. This produces an unbiased (with respect to methylation status) heterogeneous pool of PCR products. The mixed or heterogeneous pool can then be analyzed by a technique capable of detecting sequence differences (Para 0037).

Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method that Uhlmann and Nyren by using an amplification primer that does not contain CpGs as suggested by Laird. The method of Laird is advantageous because primers that lack CpG dinucleotides can be

used to amplify the sequence between the two primers, regardless of the DNA methylation status of that sequence in the original genomic DNA (Para 0016).

Response To Arguments

11. In the response filed January 17, 2008, the Applicants traversed the rejection made under 35 USC 103(a) over Uhlmann in view of Nyren. The Applicants first argument is that while Nyren's method was available as early as 1998, it was not employed for determining the methylation status of nucleotides until the inventors suggested doing so. It is noted that MPEP 2145 states that "the mere age of the references is not persuasive of the unobviousness of the combination of their teachings, absent evidence that, notwithstanding knowledge of the references, the art tried and failed to solve the problem". Further the Applicants are reminded that this is not the test for obviousness, therefore this argument is considered spurious.

Next the Applicants argue that the presently claimed method has been widely adopted in the industry and has been considered the "Gold Standard" for quantitative methylation analysis. Here the Applicants are attempting to provide evidence of secondary considerations; however they have not presented this evidence in the form of a declaration. The MPEP 2145 states that the arguments of counsel cannot take the place of evidence in the record. Therefore the argument that the Applicants method is considered the gold standard is being regarded as an opinion. Even if this evidence was in the form of a declaration, the Applicants have not provided a showing of unexpected results, commercial results, a long felt need and failure of others,

inoperability of references, skepticism of experts or copying. It is not unexpected that substituting the dideoxynucleotide sequence method for pyrosequencing would have benefits because Nyren teaches a number of advantages that pyrosequencing has over other sequencing methods such as it enables a base to be identified in a target position and DNA to be sequenced simply and rapidly while avoiding the need for electrophoresis and use of harmful radiolabels (Column 1 lines 60-64). Further the pyrosequencing method of Nyren opens up the possibility for an automated approach for large scale, non-electrophoretic sequencing procedures which allow for continuous measurement of the progress of the polymerization reaction with time. The method of Nyren also has the advantage that multiple samples may be handled in parallel (Column 9, lines 4-6). Therefore it would be expected that the method would have advantages over other sequencing methods.

Additionally the Applicants argue that a person skilled in the art would be reluctant to modify Uhlmann by using detectably labeled primers because it would interfere with the subsequent cloning steps. First of all the claims do not require a cloning step. Uhlmann teaches amplifying a nucleic acid sample, cloning the amplification product followed by sequencing. However Nyren's method eliminates the need for a cloning step since Nyren teaches that the sequencing step can be performed on PCR amplified fragments (Column 7, lines 65-67).

Regarding Claims 12 and 32 the Applicants argue that they can find no indication in the previous Office Action how these claims are made obvious by the combination of Uhlmann and Nyren. In the instant case claim 12 refers to "A method for the diagnosis

of a pathological condition or the predisposition for a pathological condition". This is a recitation of intended use of the claimed method. In order for an intended use to patentably distinguish the claimed invention from the prior art, the intended use must result in a structural difference between the claimed invention and the prior art and in the instant case it does not. Further the prior art teaches all of the active process steps required by the claims. Also the Uhlmann reference teaches an association between hypomethylation and pilocytic astrocytomas (page 1754) and Nyren teaches that pyrosequencing can be used to detect disease (Column 14, line 1-10). All of these arguments have been fully considered but are not persuasive for the reasons presented above. Therefore the rejections over Uhlmann in view of Nyren are maintained.

The Applicants also traversed the rejections made under 35 USC 103(a) over Uhlmann in view of Nyren and in further view of Herman and Uhlmann in view of Nyren and Herman and in further view of Feinberg. The Applicants argue that the deficiencies of Uhlmann and Nyren have been made of record and that neither Herman nor Feinberg alleviate these deficiencies. This argument has been fully considered but is not persuasive for the reasons presented above regarding the teachings of Uhlmann and Nyren. Therefore these rejections are maintained.

The Applicants also traversed the rejections made under 35 USC 103(a) over Uhlmann in view of Nyren and in further view of Sylvan. The Applicants argue that the deficiencies of Uhlmann and Nyren have been made of record and that Sylvan does not alleviate these deficiencies. The Applicants further respectfully submit that Sylvan's Fig 4(a) needs to be considered in conjunction with Fig 6. Here the expected allele

frequencies are plotted against the obtained allele frequencies. As can be see in Fig 6. at al expected allele frequency of 5% they actually obtained allele frequency ranges from 6% to 11%. While this may be true, claim 34 does not actually require a step of detecting an allele frequency of 5%. Claim 34 only requires detecting an allele frequency. Here the "wherein" clause is considered conditional in view of the "can be" language. Newly presented claim 39, modifies further limits claim 34 by stating that the standard deviation is not more than 1%, however again the claims do not actually require a step of detecting an allele frequency of 5% that is detected with a standard deviation of not more than 1%. Therefore this rejection is maintained.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Juliet C Switzer/
Primary Examiner, Art Unit 1634